REMARKS

By this amendment, claims 2, 10, 15, and 16 are canceled, claims 1, 3-9, and 13-18 are revised, claim 19 is added, and arguments are made to place this application in condition for allowance.

First, the claims are amended to address the objections noted in paragraph (2) of the rejection. This includes providing terms to correspond to the acronyms, removing the characterized language, identifying the sequence listing, etc. As such, the objections to the claims should be withdrawn. Claim 19 is added to further define the sequence identity.

Second, the claims are also revised in response to the rejection based on 35 USC §112, second paragraph. That is, claim 1 is revised into active tense, and the other indefiniteness issues are addressed by claim revisions. Accordingly, the rejection based on 35 USC §112, second paragraph, should be withdrawn.

Third, Applicants note the Examiner's reference to the fact that an English translation of the priority application is not of record. Since the prior art cited by the Examiner does not require Applicants to rely on the priority application filing date, no translation is required.

Fourth, claims 1 and 11 are revised to further define the invention and distinguish it over the applied prior art.

Finally, Applicants traverse the prior art rejection in light of the revisions to the claims. In review, claims 1-4, 9-14, 17, and 18 stand rejected under 35 USC §103 based on the combination of the Seyboldt et al. article (Seyboldt) and the Raghavendra

et al. article (Raghavendra). The Examiner alleges that Seyboldt teaches the features of the rejected claims but for the quantitative detection method based on the analysis of the cDNA of the GFAP by real-time PCR using amplification control and a dilution series of a reference gene. Raghavendra is cited to address this deficiency. The Examiner also cites one GenBank submission (GenBank), Bouchard, and the Lowe et al. article (Lowe) to reject claims 5, 6, and 15. Claims 7, 8, and 16 are rejected using Fahrenkrug and another GenBank submission in combination with Seyboldt and Raghavendra.

Applicants traverse the rejection on the grounds that a prima facie case of obviousness is not established in light of the revisions to the claims.

Seyboldt discloses a method for detecting bovine CNS-tissue within meat or meat-products. The method comprises, within a first step, the extraction of RNA out of a probe to be analyzed. The extracted RNA is used to generate a cDNA via reverse transcription. Dies cDNA is amplified via PCR. Afterwards the amplified cDNA is treated with restriction enzymes. The achieved restriction fragments are then used to determine within a restriction pattern analysis whether the isolated RNA contained GFAP-fragments or not.

Seyboldt therefore differs from the invention in a crucial manner. While the invention uses reverse transcription followed by real time PCR for detecting GFAP-fragments, Seyboldt uses the above described combination of reverse transcription, standard PCR and restriction fragment length pattern (RFLP)-analysis. The method described by Seyboldt thus is clearly less sensitive and therefore not suitable for making a quantitative statement.

Claim 1, as amended, differs from Seyboldt by using the cited primers and by using a TaqMan-probe spanning over the exon5-exon6-boundaries. The invention is therefore not taught by Seyboldt. The remaining question is whether the secondary references teach the features of claim 1 that are missing in Seyboldt.

A prima facie case of obviousness is not established even if Seyboldt is combined with Raghavendra. Raghavendra discloses a method comprising the RNA-extraction of a tissue-probe, the transduction of the isolated RNA into cDNA by reverse transcription and the analysis of the cDNA by real time PCR. However, Raghavendra provides neither the use of the particular primers nor the use of a TaqMan-probe spanning the exon5-exon6-boundaries of the bovine or porcine gene as is now stated in claim 1. Instead and in Raghavendra, the primers as well as the TaqMan-probe are designed for detecting the specific sequence of Rattus norvegicus. Also, the TaqMan-probe spans the exon-4-exon-5-boundary. Furthermore, the resulting product of the real time PCR performed with the primes and probe of Raghavendra is having a length of 133bp, which is rather big and thus might negatively affect the sensitivity of the real-time PCR.

Taken together, neither Seyboldt nor Raghavendra discloses the specific and, due to the shortness of the gained real time PCR-product, advantageous conditions for the method according to the invention. There is no hint at all for making the particular primers or the use of the specific exon-exon-transition obvious for the one skilled in the art.

In contrast to the Examiner's statement, the invention as now defined in claim 1 is also not obvious in view of the GenBank submissions. Both of them relate to mRNA-Sequences and it is not even possible to determine the exon-intron-structure and in

consequence the transition between the distinct exons from such an mRNA. Even if one would know the exon-exon-boundaries, it wouldn't be obvious at all to use the exon5-exon6-boundary for detecting GFAP-fragments as claim 1 requires. Seyboldt clearly teaches that the region surrounding intron 3 would be best suited for analysis. Raghavendra uses not the region of claim 1 but the exon4-exon5-boundary.

For the one skilled in the art, it is also not simple routine work to design primers which are working together and also are working together with a TaqMan-probe. Particularly, this is not a work that can be done by the simple use of a computer program, at least at the time when the application was filed and even in light of Lowe. Lowe only discloses a very rough and theoretical method for statistical determination of primers which might work together by comparing their theoretical melting temperature. It is absolutely known to the one skilled in the art that the primers obtained by the help of this program in many cases just don't work for undeterminable reasons. However, in praxis a lot of different parameters do play a role for successful establishment of working primers and there are many unforeseen problems that might occur, e.g., unusual loop formation, self-alignment, or the formation of secondary structures within the template for just naming examples. Furthermore, the program disclosed by Lowe does not teach the one skilled in the art to use the exon5-exon6-boundary for a real time PCR.

Even in light of Seyboldt, Raghavendra, one of the cited GenBank entries and Lowe (which are not less than four documents to be combined), the invention is not obvious from the standpoint of one skilled in the art. It might be known from Seyboldt to use the GFAP-fragment for detecting CNS-tissue via RNA-extraction. It might further be known from

Raghavendra to detect a GFAP-fragment isolated from rats via a combination of reverse transcription and real-time-PCR. It even might be known from Lowe what primers might all theoretically be suited to hybridize to a sequence that might be known from the GenBank entry. However, it is not taught that it is especially advantageous to use the exon5-exon6-boundary for hybridization with a TaqMan-probe nor where this exon-exon-transition is located within the sequence of the GenBank entry.

A further substantiation of the patentability of the invention is the advantages obtained by its practice. Only by using the specifically claimed combination of primer-location and TaqMan-location does a method of detection be made that is highly sensitive and reliable. Therefore, the invention provides a method of detection which is avoiding false positives but at the same time detects already small amounts of CNS-tissue contamination and thus provides safe meat to the user.

In light of the arguments made above and the revisions to claim 1, Applicants submit that a prima facie case of obviousness is not established by the cited prior art, i.e., Seyboldt, Raghavendra, GenBank, and Lowe. This prior art fails to teach or suggest the features of claim 1, including the carrying out of the real-time PCR with a pair of primers as listed in claim 1 and the $TagMan_{mbg}$ sensor spanning the boundary between exon 5 and exon 6 of the GFAP gene.

Since claim 1 is patentable over the cited prior art, its dependent claims are also in condition for allowance.

The test kit of claim 10 is also patentable over the cited prior art. Claim 10 is revised to include the limitations of claims 15 and 16 therein, which include the pairs of

primers found in claim 1. The Examiner rejects claim 15 using Seyboldt, Raghavendra, Bouchard, one of the GenBank submissions, and Lowe. Claim 16 is rejected similarly using another one of the GenBank submissions with Seyboldt, Raghavendra, and Fahrenkrug. Notably, Lowe is used to reject claim 15 but not claim 16.

In any event, neither of these rejections is valid based on the arguments made above concerning the teachings of Seyboldt, Raghavendra, the GenBank submissions, and Lowe. As such, a prima facie case of obviousness is not established against the test kit of claim 11. Since claim 11 is patentable over the cited prior art, its dependent claims are also in condition for allowance.

Accordingly, the Examiner is requested to examine this application and pass all pending claims onto issuance.

If the Examiner believes that an interview would be helpful in expediting the allowance of this application, the Examiner is requested to telephone the undersigned at 202-835-1753.

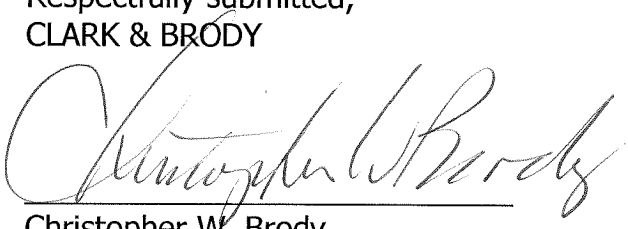
The above constitutes a complete response to all issues raised in the outstanding Office Action.

Again, reconsideration and allowance of this application is respectfully requested.

Applicants respectfully submit that there is no fee required for this submission.

However, please charge any fee deficiency or credit any overpayment to Deposit Account No. 50-1088.

Respectfully submitted,
CLARK & BRODY



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